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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/205,096	12/03/98	DRACHMAN D	01107.77737

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EXAMINER	
SORBELLO,E	
ART UNIT	**PAPER NUMBER**
1633	10

DATE MAILED: 05/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Offic Action Summary	Application N . 09/205,096	Applicant(s) DRACHMAN, DANIEL B.	
	Examiner Eleanor Sorbello	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *01 May 2000* .

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,13,15-18,20,21,23-27,29,30,32-34 and 36-40* is/are pending in the application.

4a) Of the above claim(s) *4,5,9-12,14,19,22,28,31 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,13,15-18,20,21,23-27,29,30,32-34 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 and 7* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☒ Other: *Sequence compliance* .

DETAILED ACTION

Priority

1. It is acknowledged that this application claims priority to provisional application No. 60/067, 547 filed on December 03, 1997.

Claims /Elected species

2. This office action is base on the elected species as stated in the Preliminary Amendment in response to restriction letter, received on 5/1/00.

It is acknowledged that the two species elected are (a) Fas ligand and (b) Vaccinia virus.

The following claims will be examined in this office action: 1-3, 6-8, 13, 15-18, 20-21, 23-27, 29-30, 32-34, and 36-40.

The following claims are withdrawn from consideration in this office action: 4-5, 9-12, 14, 19, 22, 28, 31 and 35, pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

3. The claims should be amended to reflect the elected species.

Sequence Compliance

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825 in response to this office action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

5. The Raw Sequence Listing supplied contains errors. An Error Report is attached.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 6-8, 13, 15-18, 20-21, 23-27, 29-30, 32-34, and 36-40, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for therapy.

The instant invention claims methods of treating patients suffering with an autoimmune disorder. Applicant's intend accomplishing this treatment by introducing a gene encoding the entire auto-antigen or portion of the auto-antigen, introduced in-vivo or ex-vivo, so as to activate the auto-antigen-specific T cells. The instant invention claims that the APC cells of the patient, into which the gene will be introduced could be administered ex-vivo into the patient for therapy. The invention also claims that the APC cells could be additionally engineered to express a Fas ligand, which specifically targets and ablates the activated T cells, (not the resting T cells), in addition to carrying a gene expressing a protein such as FADD that protects the APC cells from apoptotic destruction by the Fas ligand.

The specification teaches the modification of the mammalian expression vector $pcDNA_3$ comprising the following: (a) Sig-AChRα gene(1-210) and signaling peptide gene for processing (b)LAMP1 gene which encodes the transmembrane cytoplasmic tail which directs the antigen to the endosome processing compartment, (c) FAS ligand and

(d) truncated FADD, but does not teach one how this could be used to provide gene therapy.

Additionally, the specification fails to teach one how to construct an engineered Vaccinia virus containing the aforementioned genes.

The state of the art in gene therapy is still in its infancy and is highly unpredictable. "Clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol" (see Orkin et al. Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, distributed by the National Institutes of Health, Bethesda, MD or www. nih.gov, page 1).

Gene therapy aims to alleviate or cure diseases by altering the genetic makeup of the individual. The first clinical trials for genetic therapy were conducted in 1990. However, there is still no single outcome to point to as a success story after hundreds of clinical trials have been performed worldwide on thousands of individuals. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 2). The major problems that have been encountered are (1) the delivery of the altered genes, and (2) the inability to obtain a sustained expression of the desired protein in a specified location. (See Verma, M. et al., Gene Therapy-promises, problems and prospects, Nature Vol. 389 page 239, paragraph # 5).

Being a new field the amount of direction or guidance necessary in the specification has to be very detailed in order to provide enablement. In this case, the state of the prior art does not teach one skilled in the art how to transfer a gene and

induce a therapeutic response. Hence the specification requires detailed methods for preparation of the therapeutic compositions comprising the Vaccinia viral vector with specific dosages for specific therapies against the several autoimmune diseases claimed by the invention including Myasthemia gravis. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

The specification describes the construction of a recombinant plasmid vector containing transgenes inserted, but does not teach how these are to be used for therapy. The specification however contains prophetic statements that another vector namely the Vaccinia virus could be used for therapy. No working examples have been provided.

Further, the claims are not enabled for the expression of gene fragments. A part of a gene is unable to produce the protein of interest and therefore an expression vector containing only a part of a gene is not enabled. Furthermore, the specification does not teach any gene portions that would induce a therapeutic response.

For reasons given above, the specification does not enable one of skill in the art to make and use the vaccinia viral vector which encodes a part of a gene.

Though the specification, teaches an expression vector such as $pcDNA_3$ transfected in A20B lymphoma cells that are isolated or cultured, which kills activated T cells by means of the Fas ligand, it does not reasonably provide enablement for APC

cells transfected with the vaccinia viral vector in vivo. Nor does it teach how to use cultured cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The specification does not reasonably provide enablement for APC cells transfected with the vaccinia viral vector for invitro or invivo applications.

The specification does not teach or demonstrate making and using the vaccinia virus useful for therapy.

For reasons given above, the specification does not enable one of skill in the art to make and use the APC cells transfected with the vaccinia viral vector in vitro, or for in-vivo, or ex-vivo gene therapy applications.

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of gene therapy using the vaccinia virus. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 2, 3, 6, 7, 8, 13, 15, 16, 17, 18,20, 21, 23, 25, 26, 27, 33, 34, 36 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

Claims 1 and 2 are rejected as being vague and indefinite. The phrase 'gene which encodes all or a portion of an auto-antigen' contained in these claims is scientifically inaccurate, as a gene would not encode a partial protein. These claims should be amended accordingly.

Claim 2 and 36 are rejected as being vague and indefinite. The term 'sufficient' is unclear and will need to be defined more precisely. It is not clear what the intended meaning of the term is. It could be taken as (a) part of the gene encoding the auto-antigen is sufficient for endosomal processing or (b) the signal sequence, transmembrane and cytoplasmic tail is sufficient for endosomal processing. In Claim 36, it is not clear as to what part of the FADD protein would accomplish the function of protection. The claims should be amended.

Claim 3 is rejected as being vague and indefinite. The term 'detrimental' in the phrase, is unclear as it could be interpreted in two ways. It could be taken to mean (a) 'detrimental to activated T cell proliferation' or (b) 'detrimental to the survival of the patient. The claim should be rephrased accordingly.

Claim 16 is rejected as being vague and indefinite. The phrase 'gene transferred with a virus' could mean that the gene is transferred at the same time, and does not necessarily mean that the gene is incorporated in the virus for delivery. The claims should be amended to reflect the intended meaning.

Claims 25 , 26 and 33 are rejected as being vague and indefinite. It is unclear as to the metes and bounds of the term 'detrimental' in the claims. It is not clear if the function of the protein is to kill or prevent proliferation of the activated T cells. The claims need to be amended to convey the exact intention.

Claims that depend on the above claims namely 6, 7, 8, 13, 15, 17, 18, 20, 21, 23, 27, 34, and 38 are therefore rejected.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claims 1-2, 16-18, 24, 29-30, 32 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by August et al. (patent No. 5,633,234).

Claims 1, 2, 16-18, 24, 29-30, 32 and 37 are directed to a method of activating T cells by presenting the T cells (of patients afflicted with an autoimmune disease) with

APCs into which a gene encoding the auto-antigen (to which the patient's T cells respond) has been transfected. The said gene further comprises a signal sequence and a transmembrane and cytoplasmic tail required for endosomal processing and is introduced into the APCs via a vaccinia virus. The claims encompass steps whereby the APCs are removed, transfected with the said gene, and the cells subsequently reintroduced into the patient. It is noted that the claims do not explicitly require a therapeutic response.

August et al. taught a strategy whereby APC cells are removed from the body, cultured in vitro, subsequently transfected with an appropriate vector expressing the antigen of interest, and then re-injected into the individual. (See column 19, lines 4-13). They also taught that this method is contemplated for all immunization or vaccination strategies for diseases such as autoimmune diseases, whereby the preferred vectors suggested included the vaccinia virus. (See column 16, lines 17-35). In a further embodiment of this invention, the APCs encompass a DNA sequence expressing a transmembrane protein and a cytoplasmic protein that contain an endosomal/lysosomal targeting signal directing the protein expressed to the lysosomal membrane. (See column 9, lines 1-30). Therefore August taught all the embodiments encompassed in the claims of the instant invention mentioned above, which are therefore rejected.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J. CLARK
PATENT EXAMINER